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Transition Structures for the Reformatsky Reaction. A Theoretical (MNDO-PM3) Study.

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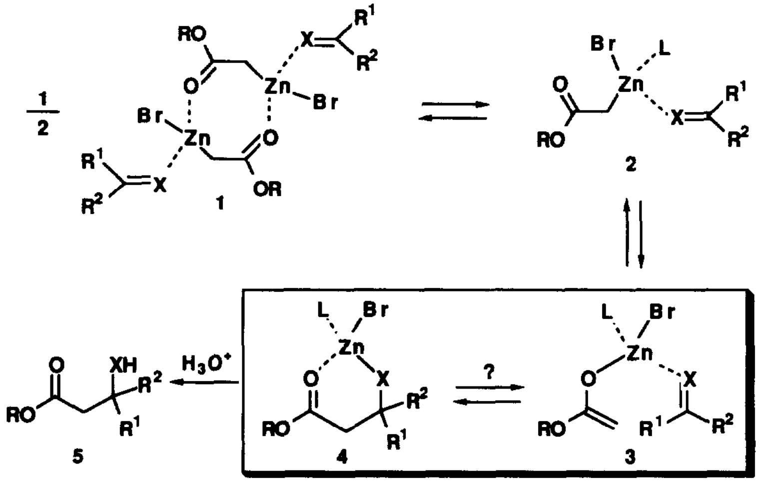
Abstract. Computational studies (MNDO-PM3) on the reaction between the Reformatsky reagent of methyl bromoacetate and formaldehyde or methanimine, predict that the Reformatsky reaction takes place preferably through a twisted boat transition state.

The Reformatsky reaction (RR) between an α-haloester and a carbonyl compound[1] or an imine[2] (the so-called Gilman-Speeter reaction) constitutes a widely used methodology of carbon-carbon bond formation. Although a variety of mechanisms has been proposed by diverse groups[1], a recent paper has reported an MNDO calculation on the minimum energy reaction path (MERP) of this important reaction[3]. The main conclusion of this paper is that, although the Refortmasky reagent **1** is in fact a dimer[4], the MERP consists in the formation of a C-metallated monomer **2**, which undergoes a (1,3) shift to give the O-metallated enolate **3** (see scheme 1). This reactive intermediate subsequently undergoes C-C bond formation through a metallo-Claisen rearrangement. According to the results of Dewar and Merz[3], the transition state associated to this metallo [3,3]-sigmatropic shift adopts a classical chair conformation.



Scheme 1. L: solvent, none; X: O, NR_3.

Since recent papers[5] have shown that the aldol and related reactions can occur *via* different transition structures (TS's), we decided to explore the profile of the RR and, in particular, the step that determines the stereoselectivity of the reaction (i.e., the **3** $\rightleftharpoons$ **4** interconversion). An *ab initio* description of the zinc atom is costly, specially with substituted, chemically significant, structures. For these cases the semiempirical molecular orbital methods have been found to yield reliable results while keeping the computational cost affordable. In particular, we decided to use the recently developed MNDO-PM3 methodology[6,7]. Two transition structures (TS's) were located on the RHF energy hypersurface corresponding to the reaction between methyl bromoacetate and formaldehyde[8]. One of these TS's corresponds to a **6a** chair like transition structure (CTS), in agreement with the result obtained by Dewar and Merz[3]. However, a second twisted boat transition structure (BTS) **7a** was also located, and it was found to be lower in energy than its partner **6a**.

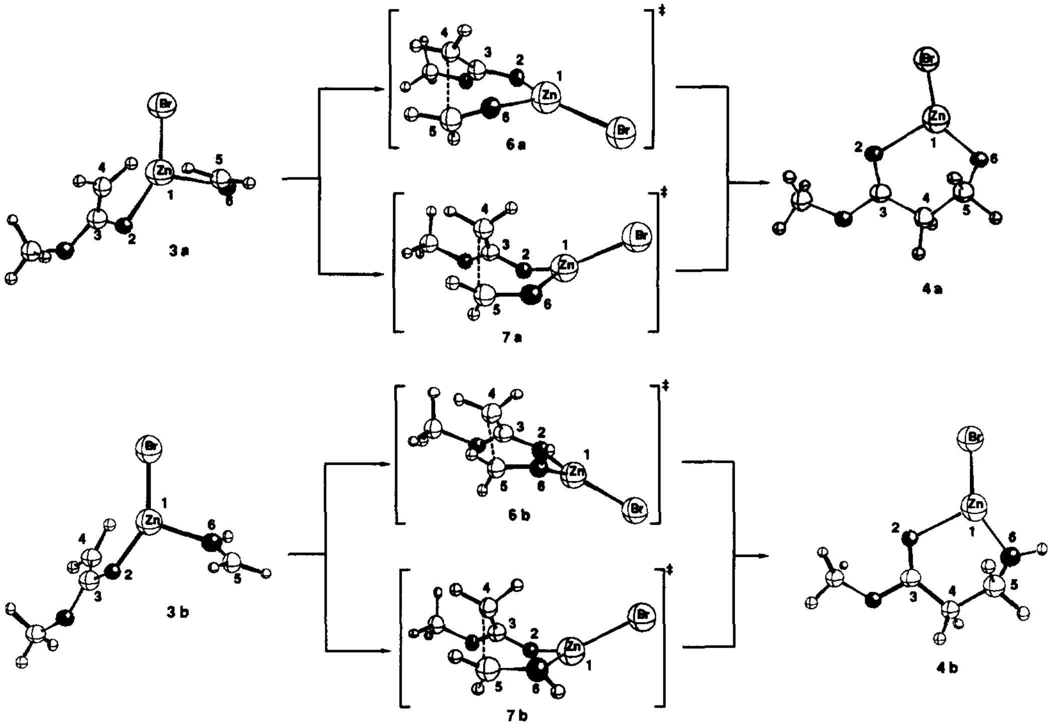


Figure 1. Calculated stationary points for the C-C bond formation step in the RR between the O-metallated Reformatsky reagent of methyl bromoacetate and (a) formaldehyde and (b) methanimine.

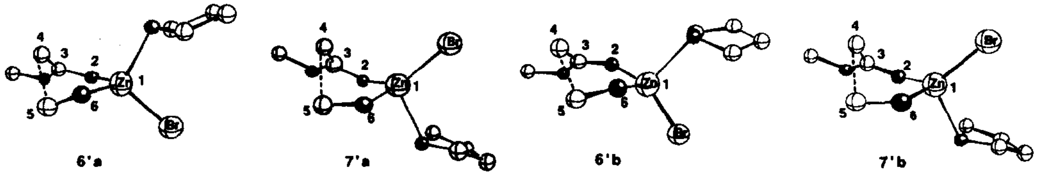
Similar results were obtained for the reaction between the Reformatsky reagent of methyl bromoacetate and methanimine. This suggests that this is a general trend regardless of the nature of the electrophile. As can be seen from inspection of Figure 1, the general features of both reactions are similar. Thus, in both cases the BTS's are *ca.* 2 kcal/mol less energetic than their CTS's analogs. This means that both processes are predicted to take place mainly *via* boat transition structures. The main structural and energetic features of the TS's **6** and **7** are collected in the Table. As can be seen from inspection of these data, the C_4-C_5 distances are in the range 2.26-2.38 Å and the angles of attack of the enolates and the electrophiles (α_N and α_E, respectively) are in good agreement with reported results corresponding to TS's of more simple enolates[5,9]. The activation enthalpies were found to be relatively low. As expected, the activation enthalpies corresponding to the simplest Gilman-Speeter reaction are higher than those obtained for the reaction between formaldehyde and the Reformatsky reagent of methyl bromoacetate. This result is in agreement with the relatively lower electrophilicity of imines with respect to carbonyl compounds.

A possible explanation for the preference of the BTS could be that in this TS the distance between the electronegative atoms 2 and 6 (see Figure 1) is higher than in the corresponding CTS and, consequently, the Coulombic repulsion should be lower in the former case[5]. However, our results show that the CTS is distorted, so that the calculated repulsion between atoms 2 and 6 turns out to be rather similar and hence does not account for the observed difference in energy between the transition structures **6** and **7** respectively. However, the bicentric terms E_{14} in the energy partitioning[10] between the Zn_1 and C_4 atoms for the TS's **6** and **7**, are very different. Thus, we have found a significant stabilizing interaction between Zn_1 and C_4 in the case of the BTS's **8**. The distances d_{14} are shorter in these TS's and the ω dihedral angles are lower (see the Table). On the other hand, the more stable complexes **3a,b** have ω values close to 0°, whereas the corresponding *s-trans* conformers (ω →180°) have been found to be *ca.* 2 kcal/mol higher in energy, the same difference found in the corresponding TS's. In the light of the above results, it is seen that the BTS's reflect better the preference for the U conformation in the corresponding O-metallated enolates **3**, because their ω values are closer to the ideal value (ω →0°). These results are in line with those reported by Houk *et al.*[5] and Hoffmann *et al.*[11] for *ab initio* calculations of aldol reactions between formaldehyde and simple enol borates or borinates.

Table. Salient properties for the transition states **6** and **7**[a,b,c]

Structure	d_{45}	E_{45}	d_{14}	E_{14}	α_N	α_E	ω	ΔH_f	$\Delta H^‡$
6a	2.372	-2.462	3.066	-1.104	97.4	100.9	29.1	-76.2	+10.8
7a	2.382	-2.562	2.666	-2.355	101.1	98.7	7.1	-78.6	+8.3
6b	2.257	-1.876	3.142	-0.532	100.1	100.0	36.4	-45.9	+18.0
7b	2.286	-1.892	2.736	-1.510	100.8	99.2	1.1	-47.6	+16.3
6'a	2.368	-2.483	2.995	-1.002	100.3	98.4	22.9	-122.6	+8.4
7'a	2.382	-2.418	2.784	-1.588	99.2	102.1	8.2	-124.0	+7.0
6'b	2.263	-1.758	3.221	-0.272	99.9	100.5	43.8	-90.0	+10.6
7'b	2.295	-1.688	2.888	-0.778	98.9	100.8	14.2	-92.2	+8.4

[a] For the numbering of the atoms, see Figures 1 and 2. All distances, angles, energies and enthalpies are given in Å, deg., eV and kcal/mol, respectively. [b] E_{AB} denotes the total of electronic and nuclear energies between atoms A and B. $\Delta H^‡$ denotes the enthalpy of activation. α_E is the bond angle C_4-C_5-X_6; α_N is the bond angle C_3-C_4-C_5 ;ω is the dihedral angle Zn_1-O_2-C_3-C_4.



6'a 7'a 6'b 7'b

Figure 2. Calculated transition structures for the RR between methyl bromoacetate and formaldehyde or methanimine in the presence of THF. Hydrogen atoms have been omitted for clarity.

It is well documented that the use of coordinating solvents in the RR can modify the stereochemical outcome of the whole reaction[1,12]. Therefore, we introduced a molecule of THF coordinated to the zinc atom in the stationary points previously located and the resulting structures were fully reoptimized and conveniently characterized. As expected, the zinc atom adopts a tetrahedral coordination with the bromine atom, the oxygen of the enolate, the heteroatom of the electrophile (nitrogen or oxygen) and the oxygen atom of the solvent. The TS's located under these conditions are depicted in Figure 2. According to the results reported in the Table, the BTS's are again earlier and of lower energy than the corresponding CTS's. The differences in enthalpy and in enthalpy of activation are similar to those found for the former case, although the activation barriers are calculated to be lower for the RR in THF. In addition, the same trends observed for the TS's corresponding to tricoordinated zinc are also found here. Thus, the BTS's **7a,b** exhibit lower values of ω and higher values of the bicentric terms E_{14}. Therefore, the explanation outlined above also applies for the case of tetracoordinated zinc atoms. It is interesting to note that the tetracoordinated zinc atom is chiral and that in both the chair and twisted boat conformations the bulky molecule of the solvent is in an equatorial disposition.

In summary, we have located for the first time twisted boat transition structures for the Reformatsky reaction in the case of both tricoordinated and tetracoordinated zinc atoms. The preference for the BTS's has been explained and it seems likely that in the RR between more substituted reactants the BTS's could play a significant role. The investigation of the stereochemical consequences of the model outlined in this paper are underway in our laboratory and the results will be reported in due course.

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7.- Both MNDO and AM1 hamiltonians were used in our investigations. The MNDO hamiltonian yields flat geometries for the TS´s, whose activation energies are slightly higher than those obtained with the PM3 hamiltonian. However, when the AM1 hamiltonian was used, we were unable to locate a CTS showing the appropriate local curvature in the corresponding hessian matrix, and only the BTS's **7a,b** could be located and characterized.

8.- All variables were optimized, and each transition structure has one negative force constant corresponding to motion along the reaction coordinate. The structures **3** and **4** have positive definite hessian matrices. All calculations were performed with the more precise SCF convergence and minimization criteria, according to the recomendations of Boyd, Stewart *et al.* (c.f. Boyd, D.B.; Smith, D.W.; Stewart, J.J.P.; Wimmer, E. *J.Comput.Chem.* **1988**, *9*, 387).

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